# Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee

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***Aims*** Paracetamol is widely recommended as the initial treatment for pain associated with osteoarthritis (OA). A sustained release (SR) paracetamol formulation (Panadol Extend$^{TM}$) was compared with standard immediate release (IR) paracetamol (Panadol$^{TM}$) in patients with knee pain secondary to OA. The primary parameter for assessment of efficacy was patient-assessed global pain relief as determined on day 8 of the treatment period.

***Methods*** A double-blind, double-dummy, randomized study was conducted. Patients ($n=403$) were treated for 7 days with paracetamol 4 g day$^{-1}$ (SR paracetamol, two 665 mg tablets taken three times daily; IR paracetamol, two 500 mg tablets taken four times daily). Patients completed daily pain measurements and assessed global pain relief at the end of the study. Therapeutic noninferiority was defined on the basis of achieving statistical noninferiority for global pain relief.

***Results*** Analysis of the primary parameter for the intention to treat population showed that the difference in proportion of patients (SR − IR paracetamol) achieving a successful response on day 8 was −0.7%; 90% CI (−8.82%, 7.45%), $P=0.890$. For the per protocol population the difference in proportion was −3.0%; 90% CI (−11.61%, 5.66%), $P=0.571$. As the lower bound of the 90% CI for the treatment difference in each case was greater than the prespecified value (−15%), SR paracetamol was considered to be statistically noninferior to IR paracetamol in terms of pain relief. The treatments were not significantly different for any of the secondary parameters in either populations.

***Conclusions*** SR paracetamol taken three times daily was statistically and therapeutically noninferior to IR paracetamol taken four times daily in patients with knee pain due to OA. SR paracetamol may be more convenient for patients with chronic pain and has the potential to enhance compliance and therefore pain relief.

*Keywords:* osteoarthritis, paracetamol, sustained release

## Introduction

Osteoarthritis (OA) is a very common rheumatic complaint and OA of the knee is the leading cause of chronic disability in developed countries [1]. Pain is the most important symptom of OA and there are several potential sources of pain within the joint [1, 2]. In addition to pain and resulting functional disability, OA has a negative effect on psychosocial measures [3]. Moreover, the overall economic impact of OA is high because the disease is common and has a moderate to high impact, as measured by its effect on employment (wage losses due to reduced function) and associated medical costs [4].

The efficacy of paracetamol 1 g four times daily has been demonstrated in a randomized, placebo-controlled, cross-over trial in patients with OA of the knee [5]. Paracetamol taken for 3 weeks was significantly more effective than placebo in relieving pain and there was functional improvement in terms of time taken to walk 50 feet. Furthermore, paracetamol 4 g daily was as effective as ibuprofen (up to 2.4 g daily) in a 4 week

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randomized controlled trial in patients with pain resulting from OA of the knee [6]. Paracetamol is recommended as the initial oral analgesic for pain management in patients with OA by respected professional organizations [7–9] on the basis of its efficacy, safety and cost. However, if patients require 4 g paracetamol daily to control pain, compliance is not easy as this necessitates a four times daily dosing regimen with standard formulations. Alternative pharmacological agents for patients who do not respond adequately to paracetamol include nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase 2 (COX-2)-specific inhibitors, but risk factors for serious upper gastrointestinal and renal toxicity need to be considered when evaluating these options [8].

A new formulation of paracetamol has been developed which combines sustained and immediate release paracetamol in a bi-layer tablet (Panadol Extend™). This formulation (denoted as SR paracetamol) has been designed to be taken three times daily, without compromising the analgesic effect. Each tablet contains 665 mg paracetamol, two tablets taken three times daily providing approximately 4 g paracetamol per day. In a recent study in patients with acute pain following surgical removal of third molars, the SR paracetamol formulation was shown to be equivalent to IR paracetamol [10]. Furthermore, the formulations were similar in onset of action and peak analgesic effect and SR paracetamol had a longer duration of activity than IR paracetamol.

The aim of the present study was to evaluate the efficacy and safety of the SR paracetamol formulation (1.33 g, three times daily) compared with standard IR paracetamol (1 g, four times daily) in treating the pain associated with OA of the knee. The study was conducted according to the principles of Good Clinical Practice and received Independent Ethics Committee approval.

## Methods

### *Patients*

All patients enrolled had a clinical diagnosis of OA of the knee, and experienced mild to moderate pain suitable for treatment with a simple analgesic. This diagnosis was confirmed by X-ray (antero-posterior view of the knee) prior to entry into the study. Patients were required to experience pain from OA of the knee on at least half of the days in the 3 months prior to the screening visit at the start of the study. The pain was to be exacerbated by movement or weight-bearing. Patients were excluded if they had received intra-articular corticosteroids within 14 days prior to screening, or if systemic steroids, NSAIDs or other analgesics were required for any medical condition.

### *Study design*

This was a multicentre, double-blind, double-dummy, randomized, parallel group, therapeutic confirmatory (Phase III) study. Patients gave their written informed consent to participate in the study.

Patients were recruited from 22 general practitioner (GP) clinics in the UK. Screened patients entered a 7 day run-in period, when they took paracetamol as required for pain relief up to a maximum of two 500 mg tablets four times daily. Baseline pain levels at the end of the run-in period were recorded, after which patients were randomized to receive either SR paracetamol ($2 \times 665$ mg tablets, three times daily) or IR paracetamol ($2 \times 500$ mg tablets, four times daily) for 7 days. Patients were stratified at randomization according to the amount of run-in paracetamol taken during the final 24 h of the run-in period ($\leq 4$ tablets and $\geq 5$ tablets) to provide an indication of pain severity. Rescue medication was provided (one or two ibuprofen tablets, 200 mg, up to a maximum of six tablets daily).

### *Treatment period*

Patients completed baseline assessments of pain and stiffness experienced within the 24 h prior to the day 0 visit. Almost all patients in the intent to treat population reported experiencing pain during the previous day (98% and 96% in IR and SR paracetamol groups, respectively). Patients started taking study medication at the first scheduled time after the baseline assessment. On days 1–7, the first dose of medication was taken at 07.00 h and the last dose of medication was taken at 23.00 h. On day 8, patients took medication up to the time of the final visit. A double-dummy dosing regimen was required to maintain the study blinding because SR paracetamol tablets are larger than IR paracetamol tablets. Fourteen tablets were taken each day at predefined times (SR paracetamol group: six SR paracetamol tablets taken at 8 h intervals plus eight dummy IR tablets; IR paracetamol group: eight IR paracetamol tablets taken at approximately 6 h intervals plus six dummy SR tablets). Patients were allocated to the treatment groups according to a randomization schedule, which was based on a block design with a block size of four.

### *Assessment of efficacy*

Pain questionnaires were completed every morning before taking study medication, for pain on waking, and sleep disturbance. Patients also answered a question every day on the duration of morning stiffness. Questionnaires were also completed every evening at 23.00 h prior to the final dose of the day, in order to record pain (during the day, on


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movement – walking on the flat, at rest) and pain relief experienced over the whole day. On day 8 (after 7 complete days of treatment), patients were asked to assess the study medication by evaluating pain relief for the whole treatment period.

The primary parameter for assessment of efficacy was the patients' assessment on day 8 of the overall level of pain relief (poor, fair, moderate, good or very good). A successful response was defined as a moderate, good or very good response. The secondary parameters were the daily assessments of the following: pain during the day, on waking, on walking, or at rest. These assessments were measured on a 5-point verbal rating scale (VRS; absent = 0, mild = 1, moderate = 2, severe = 3, very severe = 4). Other secondary outcome measures were relief from knee pain (none = 0, a little = 1, some = 2, a lot = 3, complete = 4), sleep disturbance during the night due to knee pain (number of times woken), presence and duration of morning stiffness in the knee (min), and number of tablets of rescue medication (ibuprofen 200 mg) taken for breakthrough pain.

### *Assessment of safety*

All adverse events encountered during the clinical study, whether spontaneously reported by the patient during the study or elicited by the investigator at the study visits, were reported. Blood samples were taken at the screening visit and final (day 8) visit of the treatment period for haematology and blood biochemistry.

### *Statistical analysis*

It was anticipated that 70% of patients would have a successful response with paracetamol based on a previous study [11]. Taking a response within 15% of this to indicate equivalence, approximately 150 patients per treatment group were required to provide 90% power to detect equivalent or superior pain relief based on a one-tailed test at the 5% level of significance. To allow for drop-outs, 500 patients were screened (Figure 1). Patients were considered to be compliant with study medication provided that they took at least 75% of the required number of tablets between days 1 and 7, inclusive, of the treatment period, calculated by a tablet count at the end of the study.

Prior to unblinding the data, patient eligibility for the per protocol population was reviewed based on compliance with study medication and adherence to the requirements of the protocol. As this was a study investigating noninferiority of a product, the intention to treat and per protocol populations have equal importance and their use should lead to similar conclusions for a robust interpretation. The intention to treat population included all patients who took at least one tablet of study medication and completed at least one pain assessment. The safety of the paracetamol formulations was evaluated in all of the 430 patients who entered the 7 day run-in period.

The difference between the proportion of patients who achieved a successful response on SR compared with IR paracetamol was compared by the Chi-squared test. The primary efficacy parameter (poor and fair *vs* moderate, good and very good) was also analysed by loglinear modelling incorporating factors such as whether rescue medication was taken (yes/no), the stratification variable (number of paracetamol tablets taken during the final 24 h of the run-in period) and medication. An odds ratio (odds of a successful overall response on SR relative to the odds of a successful response on IR) adjusted for significant factors in the model was produced with 90% confidence intervals.

The secondary parameters, daily pain relief and pain (during day, on waking, on walking and at rest) were analysed by one-way analysis of variance (ANOVA) incorporating terms for stratification variable, medication and stratification by medication interaction. Morning stiffness, sleep disturbance during the night due to knee pain and amount of rescue therapy required for knee pain were analysed by the Wilcoxon Rank Sum test. Baseline levels of pain (where present) were fitted as covariates in the appropriate one-way analyses. The number of patients taking rescue medication was analysed using the Cochran-Mantel Haenszel Chi-squared test adjusting for the effect of stratification.

## Results

Two efficacy populations were identified for analysis, intention to treat and per protocol. Of 500 patients screened, 430 patients entered the run-in period and 403 were randomized to treatment, all of whom were eligible for the intention to treat analysis (Figure 1). Of these patients, 349 were included in the per protocol analysis. Demographic characteristics were comparable between groups in the intention to treat population (Table 1) as was also the case for the per protocol population (results not shown). In addition, measures of baseline pain (pain on waking, on walking, at rest and during the day) were comparable between the groups in both populations. The safety population was comprised of 430 patients (Figure 1).

The main reasons for exclusion of the 54 patients from the per protocol analysis were as follows: $<75\%$ of the study medication had been taken (12 (5.9%) patients on SR paracetamol and 17 (8.5%) patients on IR paracetamol), visits occurred outside the specified time windows (11 (5.4%) patients on SR paracetamol and 13 (6.5%) patients on IR paracetamol), prohibited

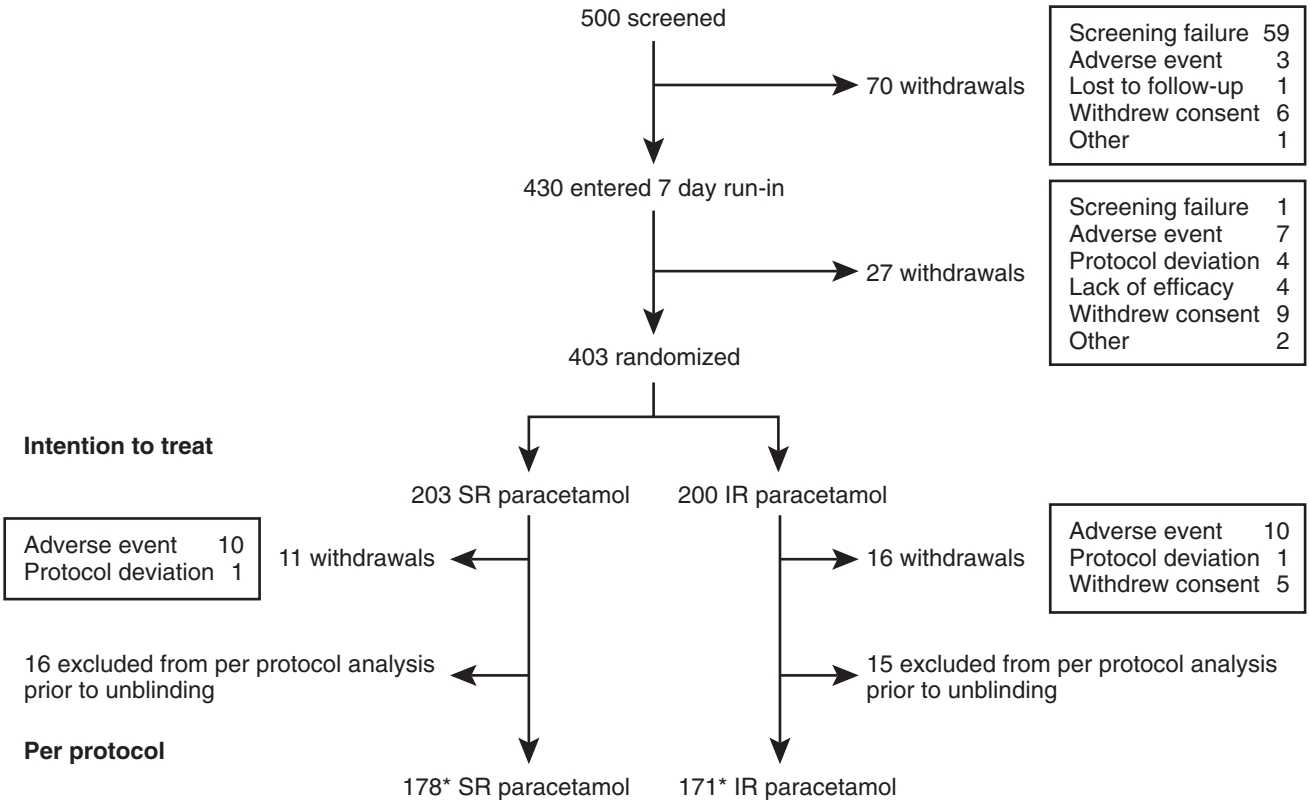


**Figure 1** Disposition of patients.

concomitant medication had been taken (7 (3.4%) patients on SR paracetamol and 4 (2.0%) patients on IR paracetamol), failed medical history (1 (0.5%) patient on SR paracetamol and 4 (2.0%) patients on IR paracetamol). Patients could be excluded for more than one reason. Compliance with study medication in the intention to treat population was good since only 29 patients (7.2%) took $<75\%$ of treatment medication.

### *Primary efficacy parameter*

The primary measure of efficacy was patient global assessment of pain relief on day 8 of the treatment period. The breakdown of the responses was similar for the two groups in both populations (Table 2). A successful response (defined as a moderate, good or very good assessment) was achieved by 58.5% of patients in the SR paracetamol group and 59.2% of patients in the IR paracetamol group for the intention to treat population. A successful response was achieved by 58.4% of patients in the SR paracetamol group and 61.4% of patients in the IR paracetamol group for the per protocol population. The lower bound of the 90% confidence interval (CI) for the treatment differences ($-8.82\%$ for the intention to treat and $-11.61\%$ for the per protocol population), was greater than the prespecified value ($-15\%$) used to define statistical noninferiority. Accordingly, SR paracetamol was concluded to be statistically noninferior to IR paracetamol ($P=0.890$ for the intention to treat and $P=0.571$ for the per protocol population, see Figure 2).

An odds ratio was calculated for overall pain relief taking into account the stratification factor, treatment and rescue medication. Non-inferiority was again concluded for the intention to treat population since the lower bound of the 90% CI for the odds ratio, 0.691, was greater than the prespecified value (0.549) used to define noninferiority for the adjusted odds ratio, assuming that SR paracetamol was 15% less effective than IR paracetamol. The odds ratio (SR : IR paracetamol) was 0.97 (90% CI 0.691, 1.369; $P=0.893$). Non-inferiority was also concluded from the per protocol analysis (odds ratio $=0.89$; 90% CI $=0.614$, 1.284; $P=0.597$).

### *Secondary efficacy parameters*

Response rates for the secondary efficacy parameters adjusted for the stratification factor (paracetamol taken in the final 24 h of the run-in) and baseline pain score for


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**Table 1** Patient demographics and baseline characteristics (intention to treat population).

| | *SR paracetamol (n = 203)* | *IR paracetamol (n = 200)* |
|---|---|---|
| Age (years) | | |
| Median | 65.2 | 65.4 |
| Range | 30.1–80.9 | 33.6–80.9 |
| Gender | | |
| Male | 79 (38.9%) | 75 (37.5%) |
| Female | 124 (61.1%) | 125 (62.5%) |
| Race | | |
| Caucasian | 202 (99.5%) | 196 (98.0%) |
| Black | 1 (0.5%) | 2 (1.0%) |
| Asian | 0 | 1 (0.5%) |
| Other | 0 | 1 (0.5%) |
| Weight (kg) | | |
| Mean | 83.16 | 81.46 |
| s.d. | 17.00 | 15.90 |
| Two most common concomitant medications* | | |
| Analgesics | 98 (48.3%) | 86 (43.0%) |
| Anti-inflammatory/ antirheumatic | 73 (36.0%) | 75 (37.5%) |
| Two most common medical histories*† | | |
| Cardiovascular | 100 (49.3%) | 95 (47.5%) |
| Genitourinary | 71 (35.0%) | 78 (39.0%) |

*Prior to start of run-in phase.
†Body system names (excluding musculoskeletal disorders).

**Table 2** Patient assessment of global pain relief.

| | *Intention to treat* | | *Per protocol* | |
|---|---|---|---|---|
| | *SR paracetamol (n = 203)* | *IR paracetamol (n = 200)* | *SR paracetamol (n = 178)* | *IR paracetamol (n = 171)* |
| Very good | 18 (8.9%) | 19 (9.5%) | 17 (9.6%) | 18 (10.5%) |
| Good | 46 (22.7%) | 41 (20.5%) | 39 (21.9%) | 37 (21.6%) |
| Moderate | 53 (26.1%) | 56 (28.0%) | 48 (27.0%) | 50 (29.2%) |
| Fair | 55 (27.1%) | 48 (24.0%) | 50 (28.1%) | 37 (21.6%) |
| Poor | 28 (13.8%) | 32 (16.0%) | 24 (13.5%) | 29 (17.0%) |
| Missing | 3 (1.5%) | 4 (2.0%) | 0 | 0 |

the intention to treat population are shown in Table 3. There were no statistically significant differences between the treatment groups for any of the parameters. Results for the per protocol population were supportive since no statistically significant differences were observed (results not shown). The actual mean/median values obtained for each treatment lie in the 'mild' to 'moderate' range for 'pain' and 'a little' to 'some' range for 'pain relief', both of which are below the centre of the 5-point VRS scales, arguing against a middle choice in the pain scales by patients.

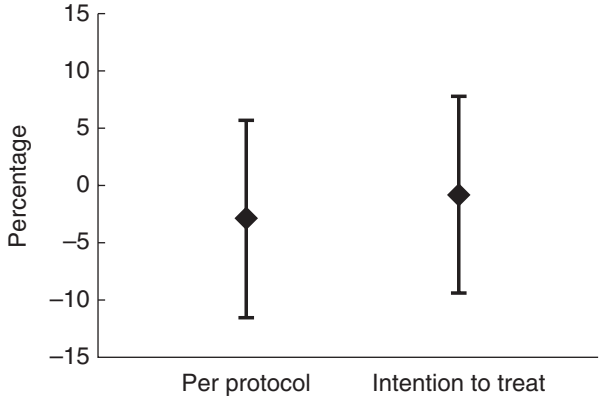


**Figure 2** Treatment differences (percentage of patients achieving a successful response with SR paracetamol – percentage of patients achieving a successful response with IR paracetamol) and 90% confidence intervals for patient-assessed global pain relief as evaluated for the per protocol and intention to treat populations. The two formulations were concluded to be statistically noninferior since the lower bound of the 90% confidence intervals for the treatment differences was greater than −15% (the prespecified value used to define noninferiority), in each population.

The median number of tablets of rescue medication taken was 0.00 in each group because most of the patients in the study did not require additional analgesia (Table 3). The majority of patients who required rescue medication (60.6%, 57/94) were in the high paracetamol usage stratification group (≥5 tablets of paracetamol taken in the 24 h prior to randomization) and were evenly distributed between the treatment groups (SR paracetamol = 61.7%, 29/47; IR paracetamol = 59.6%, 28/47). Patients in the higher usage stratification group reported greater knee pain at baseline. Out of the intention to treat population ($n = 403$), the proportion of patients taking on average ≥2 tablets of ibuprofen per day (≥400 mg) to provide additional analgesia over the treatment period was 4.5%. The proportions were similar in the SR and IR paracetamol groups (3.9%, 8/203 and 5.0%, 10/200, respectively).

### *Safety*

The distribution of adverse events between the treatment groups was similar by body system, severity and relationship to study treatment. One serious adverse event occurred during the study when a patient developed mild left hemiparesis during the run-in period, and which was considered unrelated to run-in medication. One patient with a history of food allergy and aspirin sensitivity developed a severe allergic reaction attributed to study medication (SR paracetamol) on day 5 of treatment and was withdrawn from the study. Liver tests in this

**Table 3** Analyses of secondary parameters (intention to treat population).

| *Parameter* | *Mean (median*) response* SR paracetamol (n = 203) | IR paracetamol (n = 200) | *Treatment difference* SR paracetamol − IR paracetamol | *95% CI* | P *value* |
|---|---|---|---|---|---|
| Pain during day† | 1.50 | 1.46 | 0.04 | (−0.072, 0.151) | $P=0.490$ |
| Pain on waking† | 1.13 | 1.12 | 0.02 | (−0.105, 0.139) | $P=0.785$ |
| Pain on walking† | 1.56 | 1.50 | 0.06 | (−0.066, 0.177) | $P=0.369$ |
| Pain at rest† | 1.09 | 1.07 | 0.02 | (−0.097, 0.138) | $P=0.736$ |
| Pain relief § | 1.75 | 1.71 | 0.03 | (−0.141, 0.208) | $P=0.705$ |
| Number of times woken during night* | 0.14 | 0.14 | 0.00 | (0.000, 0.000) | $P=0.630$ |
| Number of patients woken at least once | 114 (56.7%) | 103 (52.0%) | | | |
| Minutes of morning stiffness* | 0.00 | 0.00 | 0.00 | (0.000, 0.000) | $P=0.943$ |
| Number of patients with morning stiffness | 96 (47.8%) | 93 (47.7%) | | | |
| Number of rescue medication tablets taken* | 0.00 | 0.00 | 0.00 | (0.000, 0.000) | $P=0.955$ |
| Number of patients taking rescue medication | 47 (23.2%) | 47 (23.5%) | | | |

*Median.

†A score of 1–2 denotes that the level of pain was between 'mild' to 'moderate'.

§A score of 1–2 denotes that the level of pain relief was between 'a little' and 'some'.

patient were normal at screen but became clinically significant when tested 3 days after withdrawal. Alanine aminotransferase, aspartate aminotransferase and gamma glutamyl transferase (GGT) levels increased to between 5- to 10-fold above the upper limit of the reference range (ULRR); these increases were attributed to the allergic event. At follow-up (16 days after withdrawal), enzyme levels were within the reference range with the exception of GGT ($2.8 \times$ ULRR). Adverse events during the treatment phase were responsible for the withdrawal of 10 patients in each group (Figure 1). Events with two or more occurrences were as follows: headache (SR = 2; IR = 5); diarrhoea (SR = 2; IR = 2); depressed (SR = 2; IR = 0); influenza (SR = 0; IR = 2); nausea (SR = 2; IR = 2); rash (SR = 2; IR = 0); vomiting (SR = 2; IR = 0). Some patients reported more than one adverse event.

## Discussion

The SR paracetamol formulation (1.33 g, three times daily) was shown to be statistically and therapeutically non-inferior to IR paracetamol (1 g, four times daily) after 7 days treatment of pain due to OA of the knee based on patient global assessment. Therapeutic noninferiority was concluded from analyses of the intention to treat and per protocol populations. Because there was no placebo group, efficacy of the SR and IR paracetamol formulations evaluated in the present study was inferred by comparison with published data from a placebo-controlled study in patients with OA [11], taking into account differences in study design, sample size and pain rating scales.

The treatments were not statistically significantly different based on all of the secondary analyses, thus supporting the conclusion that SR paracetamol (1.33 g, three times daily) is noninferior to IR paracetamol (1 g, four times daily). Each formulation provided 4 g paracetamol day$^{-1}$, the maximum recommended daily dose approved in many European countries and in the USA and Australia, and safety profiles were similar. Rescue medication ($\geq 1$ ibuprofen 200 mg tablet) was taken by 23.3% (94/403) of the intention to treat population during the treatment period, but few patients (4.5%) took more than two ibuprofen tablets ($\geq 400$ mg) per day on average for additional analgesia. Ibuprofen 1.2 g day$^{-1}$ is recognized as an analgesic dose in patients with OA [6], therefore 400 mg ibuprofen equates to one third of this dose.

In order to maintain the study blind, patients were required to administer a total of 14 tablets daily over five dosing time points. Compliance with this dosing regimen may have been difficult to achieve had the study been of longer duration, bearing in mind that patients participating in the study were elderly. Accordingly, this simple, parallel group, two arm study was designed to demonstrate noninferiority of the new SR formulation relative to IR paracetamol.

The minimum effective plasma paracetamol concentration has been estimated as 3–5 $\mu$g ml$^{-1}$ [12, 13]. The SR paracetamol formulation was designed to have a pharmacokinetic profile such that it would rapidly deliver therapeutic plasma concentrations of paracetamol which were maintained for up to 8 h after administration of two tablets. In a steady state pharmacokinetic study with the new SR paracetamol formulation administered as in the OA study (two 665 mg tablets, three times daily), mean plasma paracetamol concentrations in volunteers remained consistently above the estimated minimum


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therapeutic concentration for paracetamol throughout the 24 h evaluation period [14, 15]. The mean $C_{min}$ in this study was 3.74 $\mu g\ ml^{-1}$ compared with 3.66 $\mu g\ ml^{-1}$ for IR paracetamol (two 500 mg tablets, four times daily). Since SR paracetamol three times daily was shown to be equivalent to IR paracetamol four times daily in the present study in patients with osteoarthritic pain and IR paracetamol retains significant analgesic activity 6 h after administration [16, 17], these results suggest that the SR paracetamol formulation provides pain relief for up to 8 h, as would be predicted from the pharmacokinetic data. In contrast, the $C_{min}$ derived from a simulated steady state pharmacokinetic profile for IR paracetamol (1330 mg, three times daily, 4 g $day^{-1}$) was 2.73 $\mu g\ ml^{-1}$ (GlaxoSmithKline, data on file), below the estimated minimum therapeutic concentration for paracetamol, suggesting that breakthrough pain may occur with this dosing regimen. The sustained release characteristics of the new paracetamol formulation are likely to account for the therapeutic equivalence of SR and IR paracetamol, not simply the dose of paracetamol administered.

To alleviate continuous pain, medications are most effective when given regularly [18]. As shown by a recent study in a cohort of women with pain associated with OA affecting the lower body, many patients taking analgesics use less than the maximum recommended dose [19]. Among those reporting severe osteoarticular pain (475 of 1002 participants), 41.2% were using less than 20% of the maximum recommended analgesic dose. Specifically for paracetamol-users, the mean daily dose was 25.6% of the maximum analgesic dose (4 g $day^{-1}$). These results underline the need to ensure that patients with pain administer therapeutic doses of paracetamol at the recommended dose frequency. It is possible that the requirement to take two tablets four times daily for standard paracetamol formulations contributes to the failure of individuals to take the maximum recommended dose. The advantage for the SR paracetamol formulation is that dose frequency is reduced but without reducing the maximum daily dose of paracetamol (4 g $day^{-1}$). A simple three times daily dosing regimen has the potential to improve compliance and hence control of pain when repeat doses of analgesic are required.

In conclusion, these results show that SR paracetamol taken three times daily was statistically and therapeutically noninferior to IR paracetamol taken four times daily in patients with knee pain due to OA. SR paracetamol may be more convenient for patients with chronic pain and has the potential to enhance compliance and therefore pain relief. The availability of a paracetamol formulation taken three times daily may help to facilitate broader adoption of professional guidelines recommending paracetamol as the oral analgesic of choice for pain associated with OA.

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